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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Art Unit: 1615
Takahide KASAI et al.	
Appl. No.: 09/514,312	Examiner: Dr. Liliana Di Nola-Baron
Confirmation No.: 8281	
Filed: February 28, 2000	Atty. Docket No.: 31671-157328
For: COATED MATERIAL AND PROCESS FOR PRODUCING THE COATED MATERIAL (as amended)	Customer No. 26694 PATENT TRADEMARK OFFICE

Letter to the Commissioner

Honorable Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Reply filed with the above-referenced Request for Continued Examination on May 26, 2004, which included two unexecuted Declarations under 37 C.F.R. § 1.132, we now submit executed copies of both of those Declarations.

Respectfully submitted,

Date: 7/20/2004

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DECLARATION UNDER 37 C.F.R. 1.132

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Takahide KASAI et al.
Serial No. 09/514,312 Group Art Unit: 1615
Filed: February 28, 2000
For: COATING AGENT Examiner: Dr. Liliana Di Nola-Baron

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Declaration Under 37 C.F.R. 1.132

Dear Sir:

Takahide Kasai declares as follows:

1. I am a inventor of the subject matter of the above-mentioned patent application.

2. I received a master degree from Osaka University, where I majored in fermentation engineering, on March, 1995.

3. I joined Kirin Brewery Company Limited(Japan) on April 1,1995, where I used to engage in research & development in the field of coatings using yeast cell walls for 3 years.

4. I have read and understood the Office Action dated August 26, 2003 and U.S. patent 5,521,089("Ishiguro"), which was cited therein as the basis for an obviousness rejection. The reference discloses methods of making microcapsules(MC) suitable for encapsulating hydrophobic liquids. In one embodiment, the MC are spread evenly on paper to form pressure-sensitive copy

paper. Like the presently claimed methods for making a coating agent, yeast cells (or yeast cell wall) are treated in various manners. However in contrast to the method of the present application, the reference dose not recognize the importance of ***not*** treating the yeast (or yeast cell wall fraction) ***with alkali.*** Furthermore, in Ishiguro's "coatings", the function of controlling the time at which dissolution of coated materials (ex. medicine) begins are not disclosed. This function is disclosed in the present application of example 5. Especially, the present invention is useful as an enteric coating agent as stated in (2) of page 32.

As, shown below, MC made by a process of the reference in which yeast are treated with alkali do not exhibit such desirable properties, whereas coatings prepared by the claimed method do exhibit such properties. For the person skilled in the art, this phenomenon was completely unobviousness over the Ishiguro reference.

More concretely, the tablet which is coated by the acid treated yeast cell wall fraction has not-releasing time (time lag) in the process of dissolution, but the tablet which is coated by the alkali treated yeast cell wall fraction dose not have not-releasing time (time lag) in the process of dissolution, because of its gradually releasing(sustained-releasing) profile. Therefore, the alkali treated yeast cell wall fraction cannot be used as time-controlled coating which is very useful in the field of drug delivery system (DDS), such as for ***enteric*** coating, and moreover, for masking bitter taste and offensive smell.

5. Under my direction and control, acid treated yeast cell wall fraction and alkali treated yeast cell wall fraction, tablets for dissolution study ,and the coated tablets were prepared in this way.

Fraction2: Acid treated yeast cell wall (This invention)

Acid treated yeast cell wall fraction (**AYC**) that was prepared by means of Example 6 in this applicantion.

Fraction3: alkali treated yeast cell wall (Ishiguro reference)

The yeast cell wall fraction obtained in the form of autolysis yeast residue in Example 1 of this application was treated according to the method described in the Ishiguro reference(Detailed description of preferred embodiments). The concrete method is as follows. The form of autolysis yeast residue in Example 1 of this application meanwhile suspended in 0.1N sodium hydroxide to a solids concentration of 5 wt%, then treated with alkali for 10 minutes at 80°C, and then centrifuged for 15 minutes at 4500rpm to remove the solubilized components, giving an alkali treated yeast cell wall fraction consisting of the resulting residue.

Preparation of core tablets

The formulation of core tablet was shown in Table 1. A mixed powder of AAP (acetaminophen) and lactose was granulated with a fluidized bed (MP-01, Powlex, Osaka) using HPC-L aqueous solution as a binder by the top spray method. The granules obtained were mixed with magnesium stearate and compressed with a rotating tabletting machine (HT-22P HATA, Tokyo) equipped with a 7mm diameter

and 4.5 mm radius of curvature die.

Preparation of coated tablets

The coating agent(fraction 2 or 3) aqueous dispersion containing 5% of coating agent(fraction 2 or 3) and 0.35% of glycerol was used for coating. The coating of core tablets was performed with Driacoater (Powlex, Osaka) at the coating % 25 based on the weight of the core tablet. The operating condition for coating were as follows: core tablets, 250 g; inlet and outlet air temperatures 70 and 45-47℃ respectively.

Table 1

The formulation of core tablet

Acetaminophen (AAP)	3.6
Lactose	112.8
Hydroxypropyl cellulose	3.0
Magnesium state	0.6
Total weigh per tablet	120.0

Release study

The release profiles of AAP from the coated tablet were studied with a dissolution tester (NTR-6100A, Toyama Sangyo, Osaka), according to the paddle method (JP13) using 500 ml of dissolution fluid at 37± 0.5℃ and a rotating paddle at 100rpm. Distilled water was used for the dissolution fluid. The quantity of AAP was determined spectrophotometrically by measuring the absorbance at 242nm.

6. The results of the analysis are shown in Table 2 and Fig1. The tablet that is coated by fraction 3 gradually releases AAP as time goes on, but the tablet that is coated by fraction 2 releases AAP after an initial time lag, and releases AAP quickly after the time lag, that is called sigmoid release curve or sigomoidal profile.

Table 2

	Start time of dissolution	End time of dissolution	Dissolution profile
core tablet	0 min	10 min	-
AYC(This invention) (fraction 2)	60 min	120 min	sigmoidal release
alkali treated yeast cell wall fraction (Ishiguro reference) (fraction 3)	0 min	1440 min	gradual release (sustained-release)

Note Base⇒ Alkali treated yeast cell wall fraction= alkali treated yeast cell wall fraction

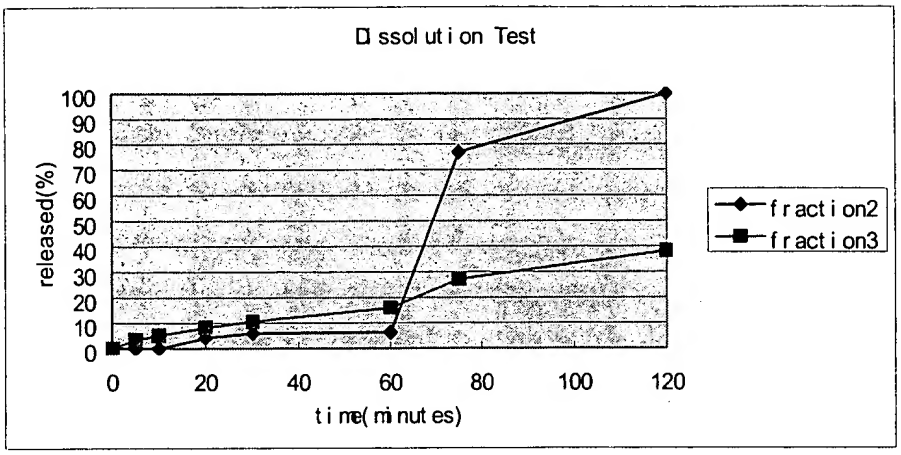

Fig. 1

7. The preceding experiments show a clear difference which would not be expected from the teachings of Ishiguro reference, and shows that the alkali treatment for yeast cell wall makes the profile of gradually releasing(sustained-release) profile, but not-alkali treatment for yeast cell wall makes the profile of sigmoidal profile.

Reportedly, the sigmoidal release profiles are obtained by *blending the polymers of different kinds or adding other materials such as a swelling agent or an organic acid* (Narisawa et al., 1996[1],1997[2]) but, the sigmoidal release profile was obtained by coating agent; ***the AYC aqueous dispersion*** of this invention.

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above referenced application or any patent issuing thereon.

1) Narisawa, S., Nagata, M., Hirasawa, Y., Kobayashi, M., Yoshino, H., 1996
An organic acid-induced sigmoidal release system for oral controllede-release preparations 2 Permeability enhancement of Eudragit RS coating led by the physicochemical interactions with organic acid J. Pharm. Sci. 85, 184-188

2) Narisawa, S., Nagata, M., Hirasawa, Y., Kobayashi, M., Yoshino, H., 1996
An organic acid-induced sigmoidal release system for oral controlled-release preparations III Elucidation of the anomalous drug release behavior through osmotic pumping mechanism. Int. J. Pharm. 148, 85-91.

Date: 28. 6. 2004

Takahide Kasai

Takahide Kasai

DECLARATION UNDER 37 C.F.R. 1.132

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In re Application of:
Takahide KASAI et al.
Serial No. 09/514,312
Filed: February 28, 2000
For: COATING AGENT

Group Art Unit: 1615

Examiner: Dr. Liliana Di Nola-Baron

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Declaration Under 37 C.F.R. 1.132

Dear Sir:

Takahiro Eguchi declares as follows:

1. I am an inventor of the subject matter of the above-identified patent application.

2. I received a bachelor degree from Kyoto University, where I majored in mechanical engineering, on March 1, 1992.

3. I joined Kirin Brewery Company Limited (Japan) on April 1, 1992, where I have been engaged in research & development in the field of coatings using yeast cell walls for more than 6 years.

4. I have read and understood the Office Action dated August 26, 2003 and U.S. patent 5,521,089 ("Ishiguro"), which was cited therein as the basis for an obviousness rejection. The reference discloses methods of making microcapsules (MC) suitable for encapsulating hydrophobic liquids. In one embodiment, the MC are spread evenly on paper to form pressure-sensitive copy paper. Like the presently claimed methods for making a coating agent, yeast cells are treated in various manners. However, in contrast to the methods of the present application, the reference does not recognize the importance of *not* treating the yeast with alkali. Furthermore, Ishiguro's "coatings" are not disclosed as air-tight, continuous, uniform and non-cracking. As shown below, MC made by a process of the reference in which yeast are treated with alkali do not exhibit such desirable properties, whereas coatings prepared by the claimed method do exhibit such properties.

5. Under my direction and control, cast films were prepared from microcapsules prepared by either of two methods exemplified in the reference or by a method of the invention.

Sample A was prepared by treating yeast with the enzyme, zymolyase 20T, and then treating the digested yeast with alkali, following the protocol of Example 3 in the Ishiguro

reference.

Sample B was prepared by treating yeast with alkali, following the protocol of Example 1 in the Ishiguro reference.

Sample C was prepared according to a method of the present invention, following the protocol of Example 6. The Resulting Acid treated Yeast Cell wall fraction (AYC) dispersed in water to a solids concentration of 8 wt%.

A cast film was made from each of the three samples as follows: each sample was placed on a thin aluminum plate and heated and dried at 120° C for 30 minutes, by means of infrared rays. The resulting films were observed visually, to determine continuity and uniformity.

6. The results of the analysis are shown in Table 1 and in Figures 1-3.

A cast film made with Sample A exhibited many cracks and voids during the drying process. The film was so fragile that its strength could not be measured. The cast film is shown in Figure 1.

A cast film made with Sample B exhibited several cracks. The film was flat and even, but was so fragile that it cracked if it was gently touched. The film was so fragile that it was impossible to attach a test piece of it to the tensile tester in order to measure its strength. The cast film is shown in Figure 2.

A cast film made with Sample C was continuous and uniform, and was non-cracking and flexible. And the film exhibits considerable tensile strength. The cast film is shown in Figure 3.

Table 1

	cracks in the film	strength of the film
MC treated by zymolyase, (prior art reference)	a few cracks many small voids	many small voids too fragile to measure
MC treated with alkali (prior art reference)	several cracks	too fragile to measure
AYC (present invention)	none	Flexible and strong

7. The preceding experiments show a clear difference which would not be expected from the teachings of the Ishiguro reference. The properties of microcapsules made by the methods of the Ishiguro reference in which yeast are exposed to alkali are clearly different from the properties of a coating agent made by the method of the present invention, in which yeast are not exposed to alkali. For example, a film made with the coating agent of the invention exhibits superior film forming ability (forms a continuous, non-cracking film) and acts as a better gas barrier (is air-tight).

8. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-referenced application or any patent issuing thereon.

Date: July 2, 2004

Takahiro Eguchi

Takahiro Eguchi